

**REMARKS/ARGUMENTS**

Reconsideration of this application is requested. Claims 1, 2 and 5-17 are listed as currently pending. Of these claims 1, 2 and 11 are under active examination and the remaining claims are withdrawn as directed to non-elected subject matter. Claims 1 and 11 are the subject of a rejection of both obviousness and also alleged anticipation; *see* items 2 and 5 of the Official Action, over the disclosures of U.S. patent 3,697,513 to Kawai while claims 1, 2 and 11 are objected to as reading on non-elected subject matter.

Applicants now address the rejections based upon prior art as stated in items 5 and 2-3 of the Official Action.

Claim Rejection 35 USC § 102

The compound of US 3,697,513 highlighted in item 5 of the Action does not anticipate the compounds of the present invention. The rejection is believed to be based on a misinterpretation of claim 1.

In fact, according to the general formula (I) of claim 1 no substitution in position  $\alpha$  with respect to the oxygen atom of the benzofuran ring can be present, since the radical Z can only be CH.

The R10 substituent is never in an alpha position with respect to the oxygen atom of the benzofuran ring and, if present, is in a  $\beta$  position with respect to the oxygen atom of the benzofuran ring.

In view of the above, applicants respectfully request the novelty objection be withdrawn.

Claim Rejection 35 USC § 103

Kawai et al is enabling only for those compounds encompassed by the claims, where the radical Y is -NHCO- which are not combretastatin derivatives.

If one considers the Kawai Patent as a whole, and since its claims do not mention the compounds of the present invention, this patent does not render obvious applicants' claims.

Moreover, the amount of description directed toward the synthesis of compounds having a radical "Y" such that the present invention is partially encompassed in the Kawai's patent is very low. Kawai's patent describes only one benzofuran vinylidene derivative. Therefore, the present invention cannot be considered obvious in light of a document which describes only one specific example bearing a benzofuran vinylidene moiety (a moiety which is known to be

important in the field of combretastatin) among some 295 specific compounds in total (from Kawai's example 1 to example 48) which are all devoid of a vinylidene moiety. In other words, one compound among 295 compounds cannot render the present claims obvious.

Furthermore, the compound described by Kawai in example 3, is also not encompassed in the present application because of the di-substituted nature of the furan moiety of the benzofuran unit. Therefore, if it would have been potentially obvious to synthesize a compound with a methyl only on this ring, this modification should have been made with the hope of maintaining the biological activity of the analogue. However, the field of biological activity that the present application deals with, is completely different from the one disclosed by Kawai.

The enablement of Kawai's patent is confined to compounds which are far away from ones to be considered as combretastatin analogues, and therefore cannot constitute inventiveness defeating prior art.

In addition, Kawai et al discloses that his compounds are used for the treatment of diseases caused by abnormal bone metabolism, as listed in column 1 lines 20-32 [osteoporosis (especially, postmenopausal osteoporosis); hyper-calcemia; hyperparathyroidism; Paget's bone diseases; osteolysis; hypercalcemia of malignancy with or without bone metastases; rheumatoid arthritis; periodontitis; osteoarthritis; ostealgia; osteopenia; cancer cachexia] because they act as inhibitors of bone resorption and bone metabolism.

On the contrary, the present application focuses on the use of the compounds of formula (I), which are combrestatin derivatives, for the treatment of diseases caused by abnormal angiogenesis, by controlling neovascularization and altering microtubule aggregation.

The above facts are confirmed by the experimental results provided in the present application, namely:

- The claimed compounds are cytotoxic to endothelial cell lines and several tumor cell lines (table 1 page 52).
- Antitumor effect is demonstrated, for example, on melanoma, lung cancer, colon adenocarcinoma, prostate carcinoma, uterine sarcoma, colorectal carcinoma, breast carcinoma.
- The effect of inhibiting microtubules aggregation is confirmed by the results in table 2 page 53.

- The anticancer activity in *in vivo* tests is shown in table 3 pages 54-55 and table 4 page 56.

The experiments also show that the claimed compounds solve another technical problem. In fact, it is known in the art that combretastatin A4-P has serious cardiovascular side effects. The evaluation of cardiovascular parameters, after administration of the compounds according to the present invention, demonstrate that they produce a therapeutic effect without causing cardiovascular side effects. This additional feature is shown in page 57.

Kawai et al do not mention angiogenesis. This means that Kawai et al also address to the therapeutic treatment of a different set of patients.

In view of the above, the skilled person could not derive the novel compounds of the present invention from Kawai et al since it suggests a different type of compounds, (not combretastatin derivatives), having a different utility.

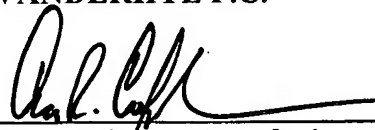
Therefore, a person skilled in the art in the field of combretastatin studies would not have considered Kawai et al as a starting point, to improve combretastatin derivatives activity. At most, this skilled person could have simply found this document casually in the course of a broad sub-structure search. Once the skilled person assessed that the subject matter of Kawai's patent was very different from that of the present application, this document would have not been considered any further.

For the above reasons it is respectfully submitted that claims 1, 2 and 11 define novel and inventive subject matter. Reconsideration, rejoinder of non-elected species and allowance are solicited. Should the examiner require further information, please contact the undersigned.

Respectfully submitted,

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